Human Neural Stem Cells Survive Long Term in the Midbrain of Dopamine-Depleted Monkeys After GDNF Overexpression and Project Neurites Toward an Appropriate Target.

Journal: Stem Cells Transl Med

Publication Year: 2014

Authors: Dustin R Wakeman, D Eugene Jr Redmond, Hemraj B Dodiya, John R Jr Sladek, Csaba Leranth, Yang D Teng, R Jude Samulski, Evan Y Snyder

PubMed link: 24744393

Funding Grants: Developmental Candidates for Cell-Based Therapies for Parkinson's Disease (PD)

Public Summary:
Preserving the wiring that prevents Parkinson's Disease. Dr. Snyder and his colleagues, in a paper published in Stem Cell Translational Medicine, tested whether overexpression of a growth factor called (GDNF) injected into the dopamine-depleted monkey striatum (one of the key areas affected in Parkinson's Disease) could enhance the integration and dopamine differentiation of transplanted neural stem cells injected at the same time into the substantia nigra (the "birth place" of dopamine neurons). Results suggested that transplantation could lead to reconstruction of portions of the nigrostriatal pathway and prove beneficial for the Parkinsonian condition.

Scientific Abstract:
Transplanted multipotent human fetal neural stem cells (hfNSCs) significantly improved the function of parkinsonian monkeys in a prior study primarily by neuroprotection, with only 3%-5% of cells expressing a dopamine (DA) phenotype. In this paper, we sought to determine whether further manipulation of the neural microenvironment by overexpression of a developmentally critical molecule, glial cell-derived neurotrophic factor (GDNF), in the host striatum could enhance DA differentiation of hfNSCs injected into the substantia nigra and elicit growth of their axons to the GDNF-expressing target. hfNSCs were transplanted into the midbrain of 10 green monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine. GDNF was delivered concomitantly to the striatum via an adeno-associated virus serotype 5 vector, and the fate of grafted cells was assessed after 11 months. Donor cells remained predominantly within the midbrain at the injection site and sprouted numerous neurofilament-immunoreactive fibers that appeared to course rostrally toward the striatum in parallel with tyrosine hydroxylase-immunoreactive fibers from the host substantia nigra but did not mature into DA neurons. This work suggests that hfNSCs can generate neurons that project long fibers in the adult primate brain. However, in the absence of region-specific signals and despite GDNF overexpression, hfNSCs did not differentiate into mature DA neurons in large numbers. It is encouraging, however, that the adult primate brain appeared to retain axonal guidance cues. We believe that transplantation of stem cells, specifically instructed ex vivo to yield DA neurons, could lead to reconstruction of some portion of the nigrostriatal pathway and prove beneficial for the parkinsonian condition.